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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/707,000	11/06/2000	Jon A. Wolff	Mirus.018.01	8513

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EXAMINER	
WILSON, MICHAEL C	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 02/18/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/707,000	WOLFF ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-9,11-14,16-22,24-26,28-31,33-36,39 and 40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,6-9,11-14,16-22,24-26,28-31,33-36 and 39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12-22-03 has been entered.

Claims 1-4, 6-9, 11-14, 16-22, 24-26, 28-31, 33-36, 39 and 40 remain pending.

Election/Restriction

This application contains claims 4 and 40 drawn to an invention nonelected with traverse. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claims 1-3, 6-9, 11-14, 16-22, 24-26, 28-31, 33-36 and 39 remain under consideration.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Applicant's arguments filed 12-22-03 have been fully considered but they are not persuasive. Again, applicants are reminded that the response should begin with support for the amendments followed by arguments regarding each rejection.

Claim R j ctions - 35 USC ' 112

I. Claims 1-3, 6-9, 11-14, 16-22, 24-26, 28-31, 33-36 and 39 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention for reasons of record.

The phrase "an injector" (claims 1, 39) does not have support in the specification as originally filed. Support cannot be found on pg 2, lines 28-29, pg 3, lines 2, 3 and 14, pg 4, lines 32, pg 5, lines 5-7, pg 10, line 20, pg 16, lines 10-16, pg 17, lines 8-31, pg 23, lines 16-23, pg 25, line 32, through pg 26, line 1 or pg 31, lines 9-12, as stated in the response filed 8-11-03, on pg 6. applicants argue the polynucleotide is to be "inserted" or "injected" into a vessel. Applicants argue the catheter and syringe needle described in the specification are a device, "or injector," with which to inject the polynucleotide. Applicants' arguments are not persuasive. It is not readily apparent that applicants contemplated using any devise for making injections as broadly encompassed by the term "injector." For example, it is not readily apparent that gold bombardment was contemplated as a means of injection.

The rejection regarding "distal to the occlusion" has been withdrawn because the specification at pg 23, lines 22-25, Example 10 and pg 32 implicitly describes injecting a solution distal to the occlusion (which is equivalent to occluding the limb proximal to the site of injection as described in the specification).

The rejections regarding "superficialis" in claim 11 and "profundus" in claim 12 has been withdrawn because it is readily apparent that flexor digitorum spf. and flexor digitorum prof. must have referred to flexor digitorum superficialis and profundus. No other flexor digitorum muscles could have such abbreviations.

II. Claims 1-3, 6-9, 11-14, 16-22, 24-26, 28-31, 33-36 and 39 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method comprising applying a tourniquet to the limb of a mammal such that blood flow of a blood vessel in the limb is occluded and administering naked DNA to said blood vessel, wherein said DNA comprises a nucleic acid sequence encoding a marker protein operably linked to a promoter and wherein said marker protein is expressed to detectable levels in muscle cells of said limb, does not reasonably provide enablement for the methods claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claim 1 requires inserting an injector into a limb blood vessel of a mammal, applying a device external to mammalian skin for occluding blood vessels in the limb, and injecting a solution of the polynucleotides into the lumen of the vessel. Claims 6-9, 11-14, 16-22, 24-26, 28, 31 and 33-36 require delivery to specific muscles within the limbs. Claim 39 requires inserting an injector into a limb blood vessel of a mammal, applying pressure using a device external to mammalian skin, injecting a solution of the polynucleotides into the lumen of the vessel, and maintaining function of the limb.

Vector targeting to desired tissues *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings available in the art of record (Miller (1995, FASEB J., Vol. 9, pages 190-199; pg 198, column 1); Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69; pg 53, 1st ¶; pg 65, 1st ¶ under Conclusion section); Verma (Sept. 1997, Nature, Vol. 389, pages 239-242; entire article; pg 240, sentence bridging col. 2-3); Crystal (1995, Science, Vol. 270, page 404-410; pg 409).

The art at the time of filing taught that not all polynucleotides injected into a limb occluded by a tourniquet were expressed in skeletal muscle. Milas (Dec. 1997, Clin. Cancer Res., Vol. 3, page 2197-2203) taught administering adenoviral particles encoding LacZ into a femoral artery and vein occluded using a tourniquet; expression occurred in hepatocytes but not in muscle cells of the limb (page 2201, col. 2, 2nd ¶).

The specification teaches injecting naked plasmid DNA encoding a marker protein to an artery of a limb distal to an occlusion and obtaining expression in muscle cells of said limb.

The specification does not enable delivering DNA to any limb as broadly claimed an obtaining expression in a muscle in a different limb. For example, the specification does not teach injecting DNA into a leg blood vessel and expressing the DNA in arm skeletal muscle. The specification does not teach delivering DNA to an arm blood vessel and expressing the DNA in leg skeletal muscle. Applicants argue it is not reasonable to interpret the claim as encompassing injection a polynucleotide into a vessel of the leg and delivering the polynucleotide to a cell in an arm. Applicants' argument is not persuasive. The circulatory system flows throughout the body, from

one limb to the other. The teachings in the specification are broad and are not limited to injecting a polynucleotide into a vessel of a limb and delivering the polynucleotide to a cell in the same limb. The examiner's interpretation of the breadth of the claims is not unreasonable. Therefore, the claims are not limited to injecting a polynucleotide into a vessel of a limb and delivering the polynucleotide to a cell in the same limb. The claims should be limited to delivering the polynucleotide to muscle cells in "said limb."

A proper determination of the combination of the location of the blood vessel injected, the type of polynucleotide (adenovirus vs. naked plasmid DNA), or the method of occlusion (tourniquet vs. clamps, balloon catheter) required to deliver a polynucleotide to a particular muscle type with a limb cannot be determined. For example, the specification does not provide any guidance for how to deliver a polynucleotide to muscle cells of the finger by injecting a vein in the upper arm. The distance would require blood flow to move the polynucleotide, but blood does not flow to the fingers in a vein in the upper arm. The specification supports this by teaching variability in expression of luciferase in arm muscles of different animals is dependent upon whether injection occurred in the radial or ulnar artery (¶ bridging pg 25-26). Table A discloses expression levels obtained in the arm (pg 26) but does not teach whether injection was in the radial or ulnar artery. No injections were performed in veins of the arm. Therefore, it cannot be determined what conditions are required to obtain the expression in muscles of the arm described in the specification. In addition, the specification does not teach how to obtain expression in muscles of the upper arm by injecting muscles of the hand with an occlusion proximal of the site of injection – the

occlusion would prevent flow of the polynucleotide into the upper arm. A proper assessment of the scope required to target the particular muscles of the arm or leg cannot be made because the specification does not provide adequate guidance. Applicants point to pg 23, lines 22-25 and pg 32, lines 12-13, 18-19 and 5, lines 13-24. while the citations describe the relationship of the occlusion to the site of injection, the citations do not describe where the limb was occluded or the polynucleotide was injected. The description is incomplete because it does not provide adequate guidance to overcome the unpredictability described in the specification in the paragraph on pg 25-26 or in the art at the time of filing.

The specification does not enable delivering DNA encoding a therapeutic protein as broadly encompassed by the claims. The specification only teaches delivering DNA encoding a marker protein operably linked to a promoter. The specification does not enable delivering any other polynucleotide or delivering DNA encoding a marker protein in the absence of a promoter. Applicants' arguments in the 2nd full paragraph on pg 10 of the response do not address the therapeutic aspect of this rejection. Applicants' arguments regarding RNA and antisense are moot as these parameters are not under consideration. Applicants do not overcome the unpredictability in the art of gene therapy established by the examiner to delivery anything more than polynucleotides encoding marker proteins by teaching the combination of promoter, vector, delivery means and level of expression required to obtain a therapeutic effect.

The specification does not provide an enabled use for mere delivery of a polynucleotide to a cell. For the delivery to have an enabled use, it must encode a

protein that is expressed to detectable levels in the cell. Therefore, the claims should recite a final step of obtaining detectable levels of expression of the protein.

Applicants argue Miller, Deonarain, Verma and Crystal do not teach the process taught by Applicants. While Miller, Deonarain, Verma and Crystal do not teach the process taught by Applicants, they do establish the state of the art at the time of filing that the ability to target the desired tissue was unpredictable. The references taught that different combinations of vectors, promoter and mode of delivery caused variable gene expression in vivo. The references also establish that the ability to obtain a therapeutic or prophylactic effect using DNA encoding a therapeutic protein was unpredictable at the time of filing.

Applicants argue Milas "did not teach: administering particles encoding LacZ into a femoral artery and vein occluded using a tourniquet and getting expression in hepatocytes but no muscle cells of the limb." Applicants' argument is not persuasive. Milas clearly taught adenovirus injected into an occluded femoral artery and vein was inadequate to obtain gene expression. Thus, occlusion was inadequate to obtain gene expression in muscles using adenovirus. Applicants do not overcome the unpredictability in the art by teaching how to obtain gene expression in muscles using occlusion and any vector as broadly claimed.

III. Claims 1-3 and 6-9, 11-14, 16-22, 24-26, 28-31, 33-36 and 39 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly

point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 1, step b) "to occlude blood vessels in the limb" is an intended use and may not occur; therefore, it is unclear whether the blood vessel is occluded. In addition, the phrase does not clearly set for the blood vessel being occluded is the blood vessel into which the injector is inserted. Applicants' arguments have been considered but are not persuasive. Just because the polynucleotide is injected distal to an occluded blood vessel does not mean it is injected into the blood vessel that has been occluded. The phrase "to occlude..." is not a clear positive step indicating occlusion has occurred (e.g. --thereby occluding blood vessels in the limb—is a clear positive step).

The phrase "external to the mammal's skin" does not clearly set forth that the device is applied to the skin; as written, it appears the device is applied anywhere outside of mammalian skin. Applicants point to pg 5, lines 13-24, which relates only to applying a cuff to the skin by touching the skin, while the claims encompass applying any device to the skin anywhere "external" to the skin. The metes and bounds of what applicants consider "external" to the skin cannot be determined. It is not readily apparent that "external to the skin" is limited to applying devices to the surface of the skin. It is unclear how the term "external" further limits the limitation of applying a device to the mammal's skin. The phrase --applying a device to the surface of the mammal's skin such that said blood vessel is occluded—would overcome this rejection.

Claim 1 remains unclear because it does not recite all the steps of the method; mere delivery of polynucleotides to cells does not have a disclosed use. The method should result in expression of a protein in a cell.

The rejections of claims 8, 9, 12, 26 and 29 regarding the term "anterior," claims 13, 14, 17, 21, 22 and 25 regarding the term "posterior" and claims 9, 14, 22 and 24 regarding the term "superficial" have been withdrawn because the art at the time of filing defined anterior, posterior and superficial muscles. See Atlas of Human Anatomy (Netter, ed. Novartis, 1989) Plates 416-422.

The phrase "wherein externally occluding blood vessels consists of compressing mammalian skin" (claim 33) remains unclear because the phrase "to occlude blood vessels" in parent claim 1 is an intended use and may not occur, and because the phrase "occluding blood vessels" lacks antecedent basis. It is unclear how "compressing mammalian skin" further limits how the blood vessels are occluded in the limb.

The metes and bounds of what applicants consider "compressing" skin remain unclear (33-36). There should be a nexus between occluding the blood vessel and applying pressure to that blood vessel by "compressing" skin, using a tourniquet, cuff or sphygmomanometer. The claims

Claims 34-36 remain indefinite because a tourniquet or cuff is not "applied over the skin." Use of the word "over" in context of a tourniquet or cuff is incorrect. A tourniquet or cuff may be applied to an arm or leg, and pressure may be applied to a blood vessel using a tourniquet or cuff, but a tourniquet or cuff is not "applied over the

skin." Applicants argue the devise must touch the skin, i.e. be applied over the skin. Applicants' argument is not persuasive. The word usage is improper. The claims are not limited to applying the devise so that it touches the skin. The phrase "over the skin" is not equivalent to "touching the skin."

The metes and bounds of "cuff" remain unclear (claims 35, 36). The term does not have a defined meaning in the art. The specification defines "cuff" as a device for impeding blood flow in a blood vessel (page 5, line 13). While a sphygmomanometer cuff can be envisioned, and the specification states tourniquets are "cuff," other cuffs cannot be envisioned. Thus, the metes and bounds of devices encompassed by the term "cuff" cannot be determined. Does the cuff have to be applied to the outside of the mammal or is a string around the blood vessel a cuff? The definition provided in the specification is confusing. Is a cuff a "device for impeding blood flow through mammalian internal blood vessels" (line 13) or a "device applied to exterior to the mammal=s skin and touches the skin in a non-invasive manner" (line 14)? It cannot be determined which definition is to be applied. Therefore, the metes and bounds of the term cannot be determined.

Claim 39, step a) remains unclear because it does not require the blood vessel is part of the mammal. While the claim requires inserting an injector "into a limb blood vessel of the mammal", the claim does not state the injector is inserted into a mammal or that the blood vessel is still in the mammal. In step a), "of" should be changed to –in— as in claim 1.

Claim 39, step a) remains unclear because it does not require the blood flow to be impeded within the mammal or within the blood vessel receiving the polynucleotide. While the claim requires "applying pressure to a blood vessel... ...by a device external to mammalian skin", the claim does not require the "mammalian skin" belongs to the mammal to which the injector is inserted, that the "device" is applied to the "blood vessel" or that the "device" is applied to the mammal to which the injector is inserted. Finally, the phrase "external to mammalian skin" does not clearly set forth that the device is applied to the skin; as written, it appears the device can apply pressure by being merely being outside of mammalian skin.

Claim 39 remains unclear because it does not recite all the steps of the method; mere delivery of polynucleotides to cells does not have a disclosed use. The method should result in expression of a protein in a cell.

Claim 39 remains indefinite because it is unclear how "wherein function is not affected by the delivery process" further limits "maintaining function of the limb." If the limb maintains function, the limb is not affected by delivery.

Applicants have not provided any arguments regarding these matters of indefiniteness of claim 39.

Claim Rejections - 35 USC ' 102

IV. Claims 1, 3, 33-35 and 39 remain rejected under 35 U.S.C. 102(b) as being anticipated by Milas (Dec. 1997, Clin. Cancer Res., Vol. 3, pages 2197-2203).

Milas taught administering adenoviral particles distally to an occluded femoral artery and vein of a rat. The femoral artery and vein were occluded using a tourniquet applied to the skin of the rat. The claims require injecting the polynucleotides thereby delivering the polynucleotides to skeletal muscles. Milas meets the limitation of the claims because the polynucleotide is injected as claimed. The limitation of "for delivering polynucleotides to a skeletal muscle cell" in claims 1 and 39 is an intended use and does not bear patentable weight because it may not occur. However, the method of Milas inherently results in delivery of the adenovirus to skeletal muscle because Fig. 3, pg 2200, shows delivery to the entire area of the leg including skeletal muscle.

Applicants argue Milas taught delivery exclusively to hepatocytes. Applicants' argument is not persuasive because the claim merely requires injection of the polynucleotides and because occluding the femoral artery using a tourniquet and injecting an adenoviral vector distal to the occlusion. Applicants argue Milas did not obtain β-gal expression in skeletal muscles. Applicants' argument is not persuasive because the claims do not require expression. Nor are the claims limited to injecting plasmids. The delivery methods of Milas are indistinguishable from those claimed. In addition, the adenovirus was delivered throughout the leg as evidenced by Fig. 3 on pg 2200. Finally, Applicants' arguments are incomplete because they do not provide any reasoning how the claims are distinguished from the teachings of Milas. A comparison of the teaching in Milas with the teachings in the specification is of little use because the

method of delivery taught by Milas is the method taught by applicants, and the claims encompass the teachings of Milas.

Double Patenting

V. Claims 1-3 and 6-9, 11-14, 16-22, 24-26, 28-31, 33-36 and 39 remain provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-42 of copending Application No. 09/707117. Although the conflicting claims are not identical, they are not patentably distinct from each other because they share similar scope of delivering polynucleotides into limb blood vessels occluded using a device external to mammalian skin for delivery to skeletal muscle cells.

VI. Claims 1-3, 37 and 39 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 6,379,966. Although the conflicting claims are not identical, they are not patentably distinct from each other because the method of '966 is an obvious species of claims 1-3, 37 and 39 in the instant application.

VII. Claims 1-3 and 6-9, 11-14, 16-22, 24-26, 28-31, 33-36 and 39 remain provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the claims of copending Application No. 09/917154. Although the conflicting claims are not identical, they are not patentably distinct from each other because they share similar scope of inserting an injector into

blood vessels of the limb, applying a device to the external skin and injecting a polynucleotide into the blood vessel.

Applicants request deference of any response to the double patenting rejection. The Patent office no longer defers a response to a double patenting rejection. The proper response to a double patenting rejection is providing a terminal disclaimer, indicating a willingness to provide a terminal disclaimer upon allowance or arguing the double patenting rejection. A request to defer the response is considered non-responsive. However, as a courtesy and to expedite prosecution, the response has been considered.

Conclusion

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at 571-272-0738.

Questions of a general nature relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

If attempts to reach the examiner, patent analyst or Group receptionist are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached on 571-272-0804.

The official fax number for this Group is (703) 872-9306.

Michael C. Wilson

MICHAEL WILSON
PRIMARY EXAMINER